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Immune Cell Molecular Pharmacodynamics of Lanreotide in Relation to Treatment Response

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BACKGROUND

Lanreotide is clinically effective in advanced neuroendocrine tumors (NETs). The inhibitory effect of lanreotide on tumor cells proliferation is due to binding to somatostatin receptors (SSTR1-5). It has been demonstrated that immune cells express SSTR1-5 differentially. The exact effect of somatostatin analogs (SSAs) on T cell function is not understood.

METHODS

In vitro and *in vivo* effects of lanreotide on immune cells were investigated, with clinical response correlates. *In vitro*, SSTR1-5 expression was measured on CD4+ T helper cells, CD8+ cytotoxic T cells, and CD4+CD25+ T regulatory cells from healthy donors (HD), and lanreotide effect on key functional immune response parameters were studied. To assess *in vivo* effects of lanreotide on immune cells of NET pts, peripheral blood mononuclear cells (n=17) obtained pre and 3 months post treatment were studied for gene and protein expression profiles in sorted T cell subsets using NanoString immune cell panel.

RESULTS

HD T cells had high expression of SSTR2 and low/no expression of other SSTRs. *In vitro*, lanreotide had no effect on functional immune response parameters investigated. For the *in vivo* study, the patient cohort consisted of 9 responders and 8 non-responders. Clinicopathological features, see table. Pretreatment immunological competence of responders was greater than non-responders, indicated by upregulation of TCR signaling (in CD4+) and interferon signaling (in CD8+ and T reg). Irrespective of clinical response, lanreotide had most significant effect on CD8+ T cells, downregulating WNT, TCR, and NF-kB signaling. Compared to non-responders, responders had downregulation of cytokine and chemokine signaling but upregulation of ubiquitination and proteasome degradation associated genes. Several myeloid specific genes were significantly changed in the CD4 T helper population, possibly due to co-isolated myeloid cells interacting with T cells during sorting.

CONCLUSIONS

The *in vivo* immune effects of lanreotide seen in the absence of *in vitro* effects reflect the relevance of environmental parameters such as interactions with myeloid components of the immune system not accounted for under the experimental in vitro conditions.

	Responders (N=9)	Non responders (N=8)
Age Median (range), y	69 (34-79)	66 (50-81)
pNET **Intestinal NET** **Unknown**	5 4 0	4 3 1
Metastatic sites N (%) **Liver** **Nodes** **Lung** **Skin** **Peritoneum**	 6 1 0 0 1	 6 2 1 1 0
Ki 67 **Not specified** **< %3** **3% - 20%** **>20%**	 1 5 3 0	 2 0 4 2
Differentiation **Not specified** **Well differentiated** **Moderately differentiated**	 1 8 0	 0 7 1

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